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**Title:** 'Folate degradation due to ultraviolet radiation: Possible implications for human health and nutrition'

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**Abstract**

Folate is essential for human health in the prevention of megaloblastic anaemia and neural tube birth defects as well as roles in cardiovascular disease and cancer. Therefore research into environmental factors that may impact folate status, such as solar ultraviolet radiation, is of great health significance. In vitro studies have shown that ultraviolet (UV) radiation can degrade folate and folic acid in human blood and this has been confirmed in several human studies. Despite these findings, there is a dearth of epidemiological research into investigating the relationship between folate status and the links to solar UV exposure.

**Key words**

Ultraviolet (UV), folate, 5-methyltetrahydrofolate (5MTHF), folic acid, photosensitisers

## Introduction

Folate is a water soluble B-vitamin that plays an important role in human health. Classically, folate deficiency is associated with an increased risk of neural tube birth defects (such as spina bifida) and megaloblastic anaemia<sup>1,2</sup>. Low folate status may also be a risk factor for some cancers and cardiovascular disease, although the role of folate in these diseases is a controversial topic with studies showing conflicting results<sup>3-7</sup>. The health impacts of low folate status necessitate the investigation of possible determinants of folate status, this research being especially important for populations most vulnerable to folate deficiency such as pregnant women and the elderly. One little known factor which may potentially decrease folate status is exposure to solar ultraviolet (UV) radiation, with research showing that UV radiation has the capacity to degrade folate in human blood and skin<sup>8,9</sup>. The relationship between UV radiation and folate degradation is complicated by the fact that UVB (Ultraviolet B, 280-315nm) radiation, while being able to degrade the main biological form of folate found in blood, 5-Methyltetrahydrofolate (5MTHF), is unable to penetrate to the dermal circulation to impact blood levels<sup>10,11</sup>. The longer wavelength UVA (Ultraviolet A, 315-400nm) is able to penetrate to the dermal circulation but is unable to directly degrade 5MTHF<sup>10</sup>. The recent discovery of an indirect degradation pathway via UVA derived generation of Reactive Oxygen Species (ROS) able to oxidise and therefore indirectly degrade 5MTHF, has however, led to renewed interest in the field<sup>10-13</sup>. Other mechanisms such as the direct degradation of the synthetic form of folate, folic acid in the blood by UVA and the effect of folate depletion in the skin from chronic UV exposure are also important pathways that appear to impact folate status in humans<sup>9,14</sup>. The public health consequences of solar UV induced degradation of folate in humans have the potential to be enormous, especially in a country such as Australia, which has high annual UV exposures<sup>15</sup>. Despite *in vitro* findings showing UV's role in the degradation of folates in the human body, there is a dearth of population based research in this potentially important area. In this review, we will provide an investigation of the major research findings in the area of UV and folate, with a particular focus on *in vivo* research and discuss the strengths and weaknesses of the major studies conducted in this important field. We will also identify existing gaps in the research and provide recommendations for possible future studies in UV and its impact of folate status.

## **Folate**

Folate is obtained exclusively from dietary intake or supplementation<sup>16</sup>. Via the small intestine, folate enters the circulation and is absorbed by cells where it is converted to active forms such as 5MTHF<sup>17</sup>. In its active tetrahydrofolate forms, its role as a one-carbon carrier is essential in methylation reactions, which include DNA synthesis (for a more detailed treatment of folate metabolism and forms please refer to Ulrich et al. 2008<sup>7</sup>)<sup>16</sup>. Folate in food primarily exists in polyglutamate forms with leafy green vegetables being a rich source of folate, however other fruit and vegetables such as broccoli, cauliflower and oranges are good sources, and liver, yeast and beer also provide a source of folate<sup>18</sup>. The synthetic form of folate used in (the majority of) supplements and food fortification is folic acid (also known as pteroylmonoglutamic acid or PGA), as this form has greater bioavailability and stability than the natural folates found in foods<sup>16</sup>. Folic acid is reduced to the active 5MTHF form, however high doses (>200 µg) result in the appearance of unmetabolised folic acid in the bloodstream before its conversion to 5MTHF<sup>19</sup>. To account for differences in higher bioavailability of folic acid compared to food folate, the Dietary Folate Equivalents (DFE) have been developed where 1 DFE = 1 µg food folate, or 0.6 µg folic acid added to food as a fortificant or 0.5 µg of folic acid taken as a supplement when fasting<sup>14,20</sup>. Many countries fortify foods with folic acid, for example, fortification of flour has been mandatory in the United States and Canada since 1998 and other countries such as Australia have also followed and introduced mandatory folic acid fortification recently<sup>21,22</sup>. The National Institutes of Health (NIH) in the United States have set the Recommended Daily Intake (RDI) for folate at 400 µg a day for adults with higher levels of 600 µg/day recommended for pregnant women to reduce the risk of neural tube defects<sup>23</sup>. Table 1 provides a summary of the folate content (as DFE) of selected foods and multivitamin supplements.

### **Health implications of folate status**

Low serum folate levels, caused by either an inadequate dietary intake or conditions such as malabsorption or liver disease, are classically associated with the development of megaloblastic (large cell type) anemia and, in fetuses of folate deficient mothers, neural tube defects (NTD's) such as spina bifida<sup>1,2</sup>. Indeed it is the prevention of NTD's, particularly following the landmark Medical Research Council's (MRC) vitamin study which showed folic acid supplementation reduced NTD risk by 72% (95% CI: 0.12-0.71) in pregnant women when taken before and following conception, that has led many countries to introduce the folic acid fortification in foods described above<sup>21,22,25</sup>.

As folate plays an important role in the metabolism of the amino acid homocysteine, which is classified as an independent risk factor for cardiovascular disease, there has been much research interest in the role of folate for reducing cardiovascular disease risk via the lowering of total homocysteine levels in the blood<sup>16</sup>. Early studies with folic acid supplementation showed much promise by significantly lowering homocysteine levels while observational studies reported significant increases in cardiovascular risk in as a result of elevated homocysteine<sup>3,26</sup>. More recent data from randomized control trials has however consistently shown a null effect from folate and other B vitamins on cardiovascular disease risk; for instance, results from a recent large meta-analysis (eight trials composed of 37,485 participants) show that homocysteine lowering intervention via vitamin B supplementation (including folate) had no statistically significant effects on cardiovascular disease risk or mortality<sup>4,6</sup>. To explain this null effect shown by the casual evidence, Blum and Smulders<sup>27</sup> have proposed an interesting hypothesis suggesting that the high levels of folic acid supplementation used in homocysteine lowering trials may lead to increased inflammation and proliferation, stimulating atherosclerotic plaque growth and destabilization. This would have the effect of negating any improvements in cardiovascular disease risk from lowering homocysteine levels.

Folate's essential role in DNA synthesis and repair has also made its role in cancer carcinogenesis of great research interest, with folate appearing to provide a protective effect on some cancers (eg. colorectal) early in carcinogenesis<sup>7</sup>. For example, a large prospective analysis of cancer mortality and morbidity in Western Australia (N=1,988) showed independent associations between decreased folate levels and increased risk of prostate cancer mortality and breast cancer morbidity over 20 years of follow up<sup>28</sup>. While adequate folate is essential to human health there is increasing focus also on the health effects of excess folate particularly in its folic acid form. The ability of folic acid to mask the haematological signs of vitamin B12 deficiency is a major concern as this can lead to a missed diagnosis and the progression of the neurological damage associated with vitamin B12 deficiency<sup>29</sup>. There is also some evidence that too much folic acid may increase risk of some cancers, for example, results from the Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial showed a 20% increased risk in breast cancer development in females taking  $\geq 400$   $\mu\text{g/day}$  of folic acid supplements compared to those not taking supplements<sup>30</sup>. Several other studies have also shown possible deleterious effects of folic acid supplementation on colon and prostate cancer, although there is a lack of consensus and evidence remains mixed in this area<sup>31,32</sup>. While the exact

mechanisms for the apparent dual health effect for folate on cancer are unknown, folate, through its role in DNA synthesis and repair, is thought to protect against cancer initiation, but once preneoplastic tumors become established, it may aid the progression of cancer<sup>29</sup>. It is important to note that even high intakes of natural folates found in food are rarely, if ever, implicated in increased cancer risk, however the paucity of quantitative folate intake data from diet makes any conclusion regarding the different health effects of folate from food versus folic acid difficult<sup>29</sup>. While there is a lack of consensus in this area, the growth of mandatory food fortification with folic acid makes further research into the possible health risks of folic acid essential.

For determining folate status, the following pathological tests are used: serum folate and erythrocyte folate. Serum folate provides a short-term assessment of folate status and thus is determinant of recent folate intake, while erythrocyte folate, provides a longer-term assessment of folate status (past 2-3 months intake)<sup>18</sup>. Traditionally, immunoassay methods are used to test folate status, however this technique is unable to distinguish between the different folate metabolites and detect the presence of unmetabolised folic acid in the circulation, thus High Performance Liquid Chromatography (HPLC) is needed when data on specific forms of folate are required<sup>19,33</sup>. The Royal College of Pathologists of Australasia uses reference ranges of 7-45 nmol/L for serum folate and 360-1400 nmol/L for erythrocyte folate, to define normal folate status<sup>34</sup>. However, both erythrocyte and serum folate status cutoffs for deficiency are poorly defined for health outcomes and various researchers have used different cutoff levels to define deficiency or 'low' folate status<sup>1,17</sup>. An example of various cutoffs to define low serum and erythrocyte folate is provided in Table 2<sup>1</sup>.

### **Folate and Ultraviolet Radiation: Overview**

With folate's role in many aspects of human health, environmental factors that may affect folate status are of great interest from a health perspective. One of these environmental factors is the photosensitivity of folates upon exposure to UV radiation. While there has been a recent upsurge of research conducted in the area of UV induced folate degradation, interest in this area is not a recent phenomenon, with Branda and Eaton<sup>35</sup> proposing a relationship between UV sun exposure and the evolution of human skin colour in 1978. Branda and Eaton<sup>35</sup> proposed that maintenance of genetic characteristics such as dark skin colour requires continuous positive selection, therefore there must be strong evolutionary pressures favoring retention of highly melanised skin in areas of intense solar radiation. The hypothesis is based on the observation that

populations with more heavily melanised skin evolved close to equatorial areas as darker skin provided these populations with a survival advantage by reducing folate and possibly other nutrient photodegradation by solar UV exposure<sup>36</sup>. Other explanations for the retention of dark skin colour, such as the protection that dark skin provides against the carcinogenic effects of UV are likely not to have impacted reproduction and therefore selection, while micronutrient deficiencies, particularly folate, are known to play essential roles in fetal development and fertility and are therefore a much more likely to drive selection pressures<sup>35</sup>. Since the publication of this article, several other authors have also published papers supporting the theory of the photoprotective role of melanised skin to reduce micronutrient degradation and its resulting impact on the evolution of human skin colour<sup>36-39</sup>. Similarly, it has been hypothesized that lighter skin provided a survival advantage away from the equator at higher latitudes, in this case by improving UV induced vitamin D synthesis, which is reduced in more heavily melanised populations<sup>40</sup>.

### **Folate and Ultraviolet Radiation: Laboratory studies**

Several experimental studies have proven that folate is vulnerable to UV degradation. For instance, *in vitro* studies have shown that folic acid (the synthetic form of folate) is photosensitive to UVA radiation<sup>13,41-45</sup>. These studies have shown that when folic acid is exposed to UVA, it undergoes photolysis and is cleaved into several photoproducts<sup>44</sup>. Laboratory studies have also shown that biological metabolites of folate found in the human body such as 5MTHF are sensitive to UVB (280-320 nm) radiation, but not UVA (320-400 nm)<sup>10</sup>. Figure 1 illustrates this by showing the absorbances of both 5MTHF and folic acid when exposed to different UV wavelengths, both UVA and UVB are absorbed by folic acid and UVB is absorbed readily by 5MTHF, however absorbance in the UVA spectrum by 5MTHF is minimal<sup>46</sup>. UVC (Ultraviolet C, 100-280 nm) radiation is absorbed by both folic acid and 5MTHF, although as it is absorbed by the earth's atmosphere it does not reach the earth's surface to affect the skin<sup>10</sup>. Thus from absorbances alone, UVB would appear to be the main UV wavelength responsible for folate degradation. This, however, does not take into account the fact that UVB does not penetrate deeply enough into the skin to reach the dermal circulation and is therefore unlikely to influence blood folate levels directly<sup>10</sup>. The longer wavelength UVA, although able to penetrate the skin to a greater depth and reach the dermal circulation, is unable to directly degrade 5MTHF, resulting in the inability of solar UV radiation to directly impact 5MTHF levels in blood<sup>14</sup>.

The recent discovery of photosensitisers such as flavins and porphyrins that

have the ability to indirectly degrade 5MTHF during UV exposure has however provided a biologically plausible mechanism for *in vivo* UV degradation of folate<sup>11,12</sup>. Both flavins and porphyrins are natural photosensitisers in human blood which produce reactive oxygen species (ROS), such as singlet oxygen, when exposed to UV radiation<sup>11,12</sup>. It is the production of these ROS that has been proposed as a mechanism that leads to the degradation of 5MTHF to the oxidized inactive form methyl 5,6 dihydrofolate<sup>12</sup>. As UVB radiation will not penetrate deeply enough into the dermis to affect circulating photosensitisers, it is proposed that it is UVA that indirectly degrades 5MTHF through the generation ROS (particularly singlet oxygen) from photosensitisers (See Figure 2 for role of UVA in folate degradation)<sup>12</sup>. Thus, combined with laboratory studies showing direct degradation of folic acid by UVA, this discovery provides a second, indirect mechanism whereby can UVA potentially degrade folate, although epidemiological studies are needed to confirm whether UV radiation *in vivo* via sun exposure or sunbeds can significantly decrease folate levels in humans.

While most of the few studies in the area are focused on blood levels of folate, folate levels in the skin are particularly vulnerable to degradation by ultraviolet radiation, both via direct photodegradation and indirect degradation via ROS<sup>9,47</sup>. The depletion of folate in skin may have significant health impacts; for instance, Williams et al.<sup>9</sup> recently conducted an experiment with a cultured keratinocyte cell model, showing that keratinocytes depleted of folate had a decreased capacity to repair DNA damage when exposed to solar simulated light. Thus folate depletion in the skin, combined with UVR exposure, appears to favor the development of the genomic instability associated with early skin carcinogenesis, a situation which was shown to be reversed by the addition of folate (in the form of folic acid) to keratinocytes which reestablished repair of DNA damage in these cells<sup>9</sup>. While the capacity of UV radiation to damage skin is not a new concept, the direct role of UV radiation in the degradation of folate in the skin and the observation of enhanced photo-and-oxidative damage in folate depleted cells requires much further investigation. The increased skin folate repletion demands caused by intense UV radiation exposure may also be another pathway leading to depletion of circulatory folate as blood folate needs to replete lost folate in the skin (see Figure 2). Further research into UV induced folate depletion of skin is therefore needed to further our knowledge of its role in carcinogenesis and the potential for decreasing circulatory folate.



### **Folate and Ultraviolet Radiation: Seasonal evidence**

There have been a number of ecological studies that have shown seasonal variation between folate levels, with lower serum folate and or erythrocyte folate reported during summer or spring compared to winter and autumn seasons where UV exposure is less<sup>48-50</sup>. Research has also shown seasonality differences in NTD's, with lower levels of NTD's reported during winter (higher serum folate) compared to summer (lower serum folate)<sup>50</sup>. Seasonality differences in cancer diagnosis and mortality have also been the focus of recent folate research<sup>46</sup>. As reported earlier, higher folate status appears to be protective in early stages of carcinogenesis, however higher folate status during later stages of carcinogenesis may decrease cancer survivability for some types of cancer<sup>29,46</sup>. Indeed, inhibition of folate metabolism plays a major role in cancer treatment with the use of chemotherapeutic agents such as methotrexate in cancer therapy<sup>51</sup>. It is through the theory of lower folate status possibly improving cancer survival at certain stages in carcinogenesis, that Steindal et al.<sup>46</sup> has proposed the hypothesis that cancer mortality is linked to seasonality via UV's role in folate photodegradation. For instance, several Norwegian studies have shown that the relative risk of death for some cancers was 20-50% lower for cases if diagnosed in summer, compared with winter (after 18 months of follow-up)<sup>51-54</sup>. Steindal et al.<sup>46</sup> suggests that lower folate status in summer resulting from increased solar UV folate degradation is a possible reason for the improved cancer prognosis seen in these studies. While these studies were primarily investigating the role of vitamin D and seasonality in cancer prognosis, the Norwegian data provides an interesting alternative hypothesis, particularly considering folate's important role in cancer. It is also important to consider that both hypotheses are not mutually exclusive; for instance, both higher vitamin D and lower folate status in summer may contribute to the improved cancer prognosis seen in ecological research designs. Further investigation in this important area is therefore needed into how solar induced degradation of blood folate may be a factor in improving prognosis in some forms of cancer or preneoplastic tumors.

### **Folate and Ultraviolet Radiation: Sunbed and Solar Ultraviolet studies**

There have only been a few small population-based studies conducted into UV induced folate degradation (See Table 3). These include a study Gambichler et al.<sup>55</sup> showing that both single and serial exposure to UVA radiation via a sunbed did not significantly affect serum folate levels in healthy participants. Small study numbers (N=24; with only eight volunteers exposed to UVA radiation) and the use of UVA radiation, which is not able to photodegrade 5MTHF-the main form of

circulatory folate in the human body may have impacted the results. While the study undertaken by Gambichler et al.<sup>55</sup> agrees with the laboratory data showing that 5MTHF is not vulnerable to direct photodegradation by UVA (although some indirect degradation may have been expected), other forms of folate may be more susceptible. For instance, the finding that folic acid is sensitive to UVA irradiation is extremely important due to the use of this form for supplementation and food fortification. The findings from *in vitro* studies reported earlier, showing higher UVA absorption in folic acid compared to 5MTHF, led Fukuwatari et al.<sup>14</sup> to hypothesise that humans taking folic acid supplements would be at increased risk to degradation of folate by sunlight (via UVA exposure). To test this hypothesis, a series of experiments were conducted using a sample of Japanese college students aged between 21-24 who were asked to bathe in sunlight between 11am to 1pm, while also taking 0.25 mg of folic acid supplements at each meal for two days prior to, and once on the day of blood testing<sup>14</sup>. Folate concentrations were decreased when participants (n=7) bathed in sunlight, while when participants were not exposed to sunlight, folate concentrations remained the same (for participants exposed: plasma folate pre-test =38.0±7.2 nmol/L vs. post-test =28.1±4.6 nmol/L)<sup>14</sup>. The studies also showed no difference in plasma folate post sun exposure when folic acid was not taken as supplements by participants. This corresponds to the data collected by Gambichler et al.<sup>55</sup> and *in vitro* studies showing no significant absorption and degradation of 5MTHF by UVA irradiation. While there are several limitations in the study by Fukuwatari et al.<sup>14</sup>, particularly the small study numbers and lack of randomisation, data collected from the study points to the possibility that people supplementing with folic acid are at greater risk of folate degradation than those who are not. This is of particular concern for pregnant women (especially with high sun exposure) who often obtain a significant proportion of their folate intake from folic acid supplementation<sup>16</sup>. The data from both of these studies also raises questions about the degree of the *in vivo* impact of indirect degradation of 5MTHF via generation of ROS, as they showed no significant change in folate status following UV exposure (with the exception of the significant change if folic acid was taken)<sup>14,55</sup>.

Several studies have also examined the effect of UVB radiation exposure on folate status by using psoriasis patients where UVB radiation therapy is often used as a treatment<sup>56</sup>. Narrowband UVB phototherapy was used to investigate the effect of UVB on serum and erythrocyte folate status in patients with psoriasis by Rose et al.<sup>57</sup> (N=35); and in a mixed sample of dermatological patients by Cicarma et al.<sup>58</sup> (N=19), although no effect was observed in either of these studies. An earlier study by Shaheen et al.<sup>59</sup>, however reported a significant 27%

decrease in serum folate following exposure of 20 vitiligo patients to 36 narrowband UVB sessions. All three studies used similar equipment with the UVB source provided by standard narrowband UVB bulbs (Philips TL-01 fluorescent lamps) which have an emission peak of 311 nm. One likely explanation for the differences is the larger number of phototherapy sessions and higher cumulative UVB exposure used in the Shaheen et al.<sup>59</sup> study to treat the exposure group<sup>60</sup>. It is also worth noting the different types of dermatological conditions used in each these studies may have also affected results, however little research is available into how any these conditions may impact vulnerability of folate to ultraviolet radiation.

To test the effect of broadband UVB exposure (280-400 nm), a recent study was conducted by Juzeniene et al.<sup>33</sup> in which both erythrocyte and serum folate were measured via a series of experiments in both healthy volunteers and psoriasis patients in Oslo, Norway. Both broadband UVB exposure from sunbeds and sunlight exposure during summer were shown to have no influence on healthy participants, however a small decrease in folate level was observed in psoriasis patients following broadband UVB exposure<sup>33</sup>. Once again small study numbers (N= 5 to 13) and the lack of measurement of dietary and supplemental folate intake (to allow controlling for) in the sample are some limitations. Also, as noted by Juzeniene et al.<sup>33</sup>, the use of HPLC rather than the more standard immunoassay method for analysing erythrocyte folate would have allowed the observation how UVB and sunlight affected different folate fractions such as 5MTHF, folic acid and the oxidised methyl 5,6 dihydrofolate. This study, combined with previous research, is important as it provides evidence that only very high doses of UVB are required to photodegrade 5MTHF. As UVB is unable to penetrate to the dermal circulation it is possible that skin derived depletion of folate (see figure 2) or possibly another mechanism; for instance, an increased vulnerability to UVB in people with some dermatological conditions is responsible for this degradation.

With so few epidemiological studies conducted, the ability of sun exposure to affect folate status in clinically significant levels, that would impact human disease, is impossible to ascertain. There is also conjecture as to whether UV sun exposure's impact on folate status would have provided the necessary selection pressure to provide a role in the evolution of human skin colour. Research in countries with higher UV intensities and exposures may be an important next step, as most of the epidemiological research has been conducted in higher latitudes where UV intensities even in summer are quite low.

## Conclusion

The question of whether UV radiation can affect folate status in clinically significant levels *in vivo* is of great health importance. While laboratory findings have allowed us to elucidate possible mechanisms of UV induced folate degradation and ecological studies have pointed to possible health effects from UV induced folate degradation, *in vivo* data has shown mixed results. Population-based studies have mainly focused on the use of sunbeds with only a few studies testing the impact of solar UV exposure on folate status. Further complicating matters is the lack of consensus regarding folate reference ranges and the need to measure different types of folate due to the varied impacts of UVA and UVB radiation on the different forms of folate, such as 5MTHF and folic acid. However, recent findings showing UV photodegradation of the synthetic folic acid *in vivo* when people are exposed to solar UV is of great health significance due to the introduction of mandatory folic acid fortification in food for many countries and the reliance, particularly of pregnant women, on folic acid supplementation to provide a significant proportion of their folate needs.

Larger epidemiological studies are really needed that will allow researchers to observe the effects of UV on the folate status of free-living individuals. These larger studies would build on the research already conducted in this area and would enable researchers to observe any statistically significant population level affects between solar UV exposure and folate status. This, combined with a research emphasis on groups who are most vulnerable to folate deficiency, for example, pregnant women taking folic acid supplements, would provide much needed data into the possible consequences of folate photodegradation on human health. Improving our understanding of the various mechanisms of UV induced folate degradation in blood will also be important as this would allow the elucidation of the relative contributions of direct and indirect UVA mechanisms of photodepletion of folate. The impact of folate depletion in the skin by both UVA and UVB radiation and its impact on skin cancer as well as contribution to decreased blood folate status via increased skin folate demands is another area of folate research in need of further investigation.

Future studies need to consider appropriate folate assay methodology as research has shown varying impacts of UV radiation on different forms of folate. For instance, much of the current research has focused on measurement of blood levels of 5MTHF, while other important metabolites such as folic acid, which is more vulnerable to UVA degradation, are rarely tested or not distinguished in standard serum folate and erythrocyte folate assays. Thus the use of assays which allow researchers to distinguish between different folate

metabolites will be important. Another important consideration is that so far much of the interest and conduct of folate and UV research has been largely confined to Northern Europe and Japan, regions where populations experience significantly less UV exposure than countries such as Australia, so research into the effects of sunlight exposure on the folate status of populations in high UV environments is a priority. Future research into this field will also benefit greatly if dietary and supplemental folate intake is also collected, as both the type and amount of folate consumed have major implications for UV and folate studies.

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Table: 1 Dietary Folate Equivalents (DFE's) of selected foods and supplements

Food	DFE's (µg) per 100g	Weight/serving to provide RDI (400 µg/day)
Wholemeal Bread (fortified-Australia)	248	160g (approx. 5 slices)
Asparagus (cooked)	133	300g (approx. 20 spears)
Spinach (cooked)	105	381g (approx. 4 cups)
Orange	31	1300g(approx.12 oranges)
Lentils (cooked)	182	220g (approx. 1 cup)
Beef Liver	218	183g
Multivitamin supplement	200-500 per capsule/tablet	1-2 capsules/tablets

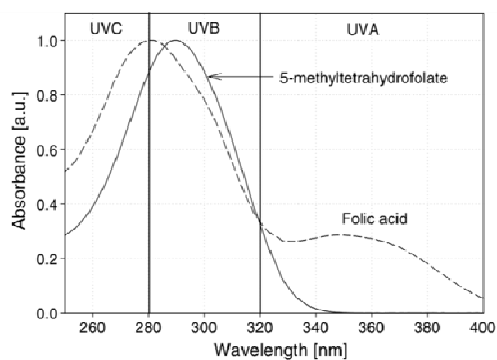
(Sutor and Bailey<sup>20</sup>, FSANZ<sup>24</sup>)

Table 2: Classification of low and normal serum and erythrocyte folate levels

Classification	Serum folate (nmol/L)	Erythrocyte folate (nmol/L)
'Very low'	<6.8	<370
'Moderately low'	6.8-<11.0	370-<513
'Normal'	≥11.0	≥513

(Data from Flood et al.<sup>1</sup>)

Figure 1: Absorbances for UVA and UVB radiation in 5MTHF and Folic Acid



(Sourced from Steindal et al.<sup>46</sup>)

Figure 2: Proposed pathway for blood folate degradation in human blood and skin

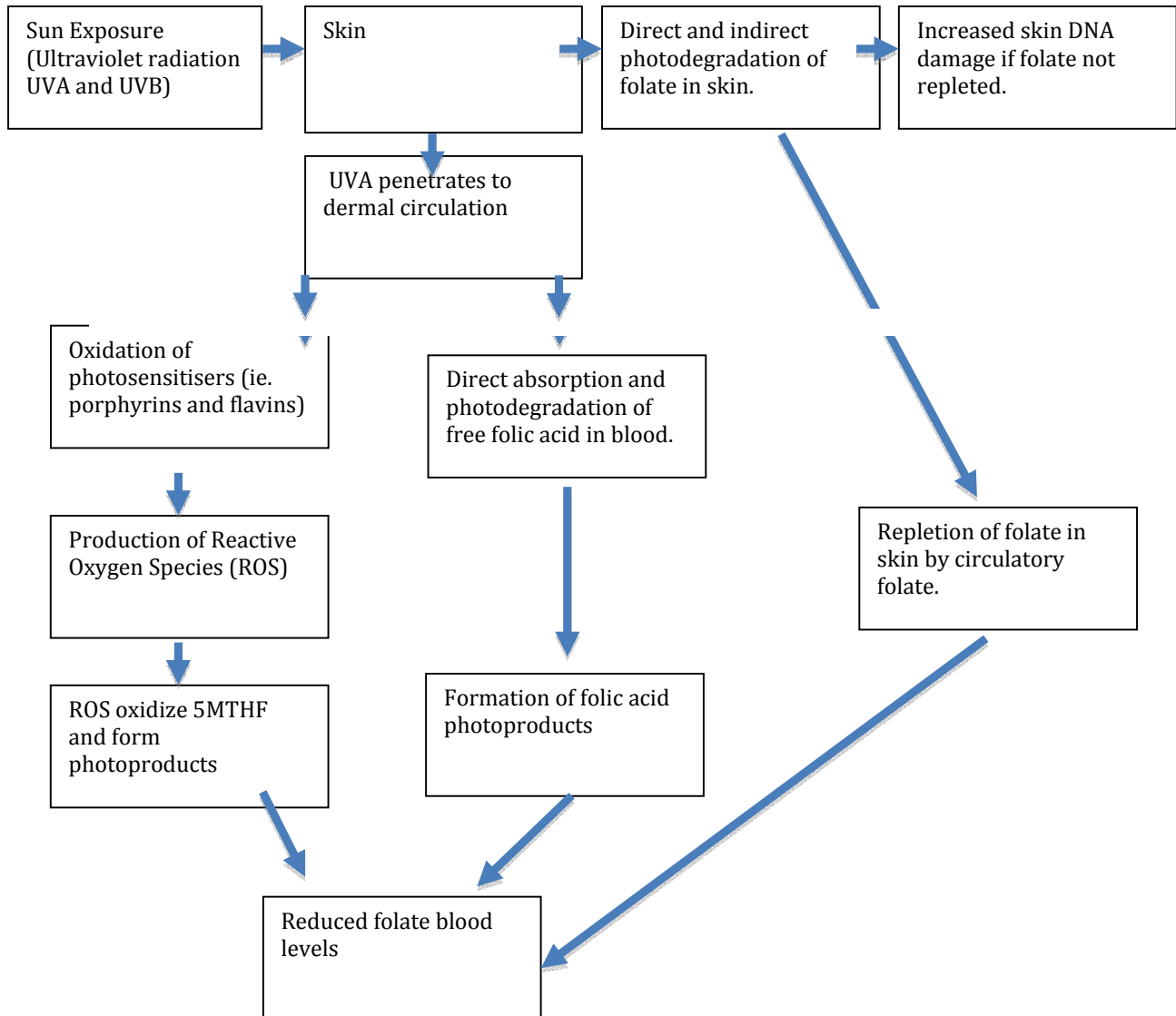


Table 3: Published in vivo studies in folate degradation and UV exposure

Author (Country study conducted)	Radiation treatment /cumulative dose (unless otherwise specified)	Blood Testing protocol	Study participants	Results
Gambichler et al. <sup>55</sup> (Germany)	UVA from sunbed twice weekly for 3 weeks/96J cm <sup>2</sup>	Serum folate tested with automated immunoassay	N=24 healthy participants; n=8 participants randomised into UVA treatment group	No significant differences in serum folate observed between exposed and non-exposed groups.
Shaheen et al. <sup>59</sup> (Egypt)	Narrowband UVB with 36 exposures/ 76J/cm <sup>2</sup>	Serum folate tested by HPLC	N=40 vitiligo patients ( n=20 study group; n=20 control)	Significant decrease in serum folate following UV treatment (baseline 18.3 ± 5.9nmol/L vs. 13.4 ± 3.4nmol/L after UV).
Fukuwatari et al. <sup>14</sup> (Japan)	Solar UV from outdoor exposure 11.00-13.00 for two days in summer/ UVA: 12 J/cm <sup>2</sup>	Serum folate tested with microbioassay	N=7 female students taking 0.25 mg of folic acid supplements at each meal for 2 days and morning of blood test. Control: same protocol and participants but no sun exposure on another day	Significant decrease in serum folate following sun exposure (38.0 ± 7.2 nmol/L vs. 28.1 ± 4.6 nmol/L).
Rose et al. <sup>57</sup> (United Kingdom)	Narrowband UVB with minimum of 18 exposures/UVB average 2.3 J cm <sup>2</sup> per visit (Note: dose varied depending on participants clinical response to UVB phototherapy).	Serum and erythrocyte tested with immunoassay	N=35 psoriasis patients	No significant decreases in serum or erythrocyte folate following UVB exposure.
Cicarma et al. <sup>58</sup> (Norway)	Narrowband UVB from photocabinet with a total of 9-15 treatments/ 2.35-13.4 J/cm <sup>2</sup> (Note: dose varied depending on participants skin type and clinical response to UVB phototherapy).	Serum and erythrocyte folate with immunoassay; 25(OH)D with radioimmunoassay	N=19 dermatological patients	Significant increase in 25(OH)D but no effect on blood folate status
Juzienne et al. <sup>33</sup> (Norway)	<b>Study 1</b> : Solar UV from outdoor exposure/UV not measured <b>Study 2</b> : UV from sunbed 4 sessions 2x 10 min and 2 x 20min <b>Study 3</b> : Broadband UVB photocabinet single exposure/ UVB 0.18-0.46 J/cm <sup>2</sup> ;UVA 0.04-0.46 J/cm <sup>2</sup> <b>Study 4</b> : Broadband UVB photocabinet 7-22 exposures/ varied dose (maximum dose 115-220J/cm <sup>2</sup> ).	Serum and erythrocyte folate; homocysteine and 25(OH)D	<b>Study 1</b> : N=17 (4 psoriasis patients and 13 healthy participants). <b>Study 2</b> : N=6 healthy males <b>Study 3</b> : N=9 psoriasis patients <b>Study 4</b> : N=10 psoriasis patients	No statistically significant effects of solar or artificial UV exposure on blood folates in all 4 studies. Slight reduction in blood folates reported in psoriasis patients.

